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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Attachment

The rejection of Claims 1, 3-4 and 6-15 under 35 U.S.C. 102(e) as being anticipated by Chtarto et al. (US 6,780,639, filed 8/24/2004, of record) is maintained for reasons of record and herein. In addition, the proposed claim amendment which adds the modifier "eukaryotic" does not simplify or further limit the claims because the claims are already drawn to "animal" which is more limiting than the proposed addition of the term "eukaryotic".

Applicants arguments have been fully considered but are respectfully not found persuasive because currently amended claims 1, 3-4 and 6-15 are drawn to a bidirectional promoter (in the context of a gene transfer expression vector containing an expression cassette/construct; Claims 4 and 6-15) for expression of at least two coding sequences in opposite direction in animal cells comprising 5' end to 3' end: (a) a first minimal promoter sequence of cytomegalovirus (CMV) or mouse mammary tumor virus (MMTV) genomes; (b) a promoter sequence of an animal gene comprising an enhancer region and a second minimal promoter sequence (can be phosphoglycerate kinase or ubiquitin; claim 3); the two promoter sequences driving a coordinate transcription of said coding sequences in the opposite orientation. The cassette of Claims 4/6 further comprises insertion sites downstream to each promoter and polyadenylation sites downstream of the insertion sites and at least one IRES sequence (to express three or more genes). The vector of Claim 9 further comprises lentiviral or retroviral sequences. Claims 10-15 are drawn to the use of the construct of Claim 9 for delivery and expression of multiple genes in animal (human) cells (neurons) ex vivo.

Chtarto et al. (see whole document, particularly Fig. 6, columns 5-8, Example 3, Claims 1-13) teach expression vectors (which can contain AAV or retroviral sequences) comprising a bi-directional promoter comprising two minimal CMV promoters (mini CMV promoters) oriented in opposite directions as well as insertion sites for foreign sequences, polyadenylation sites downstream of the insertion sites and at least one IRES element. Chtarto et al. also recite use of the construct for delivery and expression of multiple genes in re-transplantable animal (human) cells (can be neurons) wherein the cells can be ex vivo. The tet operator sequences present between the minimal CMV promoters act as an enhancer. Chtarto et al. therefore teaches the claimed invention.

Applicants argue that Chtarto et al. is "directed exclusively to a vector comprising a bi-directional antibiotic controlled activator-responsive promoter", further stating that the promoter of Chtarto et al "comprises a tetracycline (Tet) responsive element". Applicants further define a Tet responsive promoter as the following:

> The Tet responsive promoter is a synthetic sequence composed of 7 repetitions of an 8 nucleotide-long prokaryotic sequence. Such promoter is not able to exploit the endogenous mammalian transcriptional machinery in order to work properly. Therefore, to render this promoter functional, it is necessary to express an additional transgene encoding for a chimeric transcriptional activator composed of two halves, the first one being of prokaryotic origin and the second one being of viral or human origin.
>
> A fundamental feature of the tetracycline-responsive expression system is that the promoters used must be insulated from nearby competing enhancers in order to prevent inappropriate transactivation and preserve integrity of modulation by doxycycline. Therefore, only minimal promoters have been so far used in this system. Moreover, the Tet-regulated system depends on the expression (or exogenous administration) of transactivators, whose expression (or administration) may encounter problems in vivo.

Thus, Applicants argue that in contrast, the present invention is "directed to synthetic eukaryotic bidirectional promoters, based on the juxtaposition of a core promoter element placed upstream and in opposite orientation to an efficient promoter, that exploits the endogenous transcriptional machinery available to most animal cells types to drive robust expression of two divergent transcripts". Applicants further argue that the "fact that the bidirectional promoter of the present invention comprises a minimal viral promoter and a full length animal promoter represents a fundamental difference over the prior art in general, and over Chtarto et al in particular". In addition, Applicants submit that it is "well known in this art that the eukaryotic and prokaryotes promoters act differently", reciting the following:

> The promoter contains specific DNA sequences, response elements, that are recognized by proteins known as transcription factors. These factors bind to the promoter sequences, recruiting RNA polymerase, the enzyme that synthesizes the RNA from the coding region of the gene.
> • In prokaryotes, the promoter is recognized by RNA polymerase and an associated sigma factor, which in turn are brought to the promoter DNA by an activator protein binding to its own DNA sequence nearby.
> • In eukaryotes, the process is more complicated, and at least seven different factors are necessary for the transcription of an RNA polymerase II promoter. See **Exhibit A, 5 pages**.

In addition, Applicants state that "it is well known from general biology text books that a promoter of a prokaryote organism cannot work in the environment of an eukaryote organism and vice versa". Applicants further argue that "[t]he bidirectional promoter of the present invention can be based on any eukaryotic promoter: ubiquitous, constitutive, tissue specific or endogenously regulated". Applicants further submit that:

> In nature, few instances of bidirectional promoters have been documented and only very recently recent surveys of the human genome have indicated an abundance of divergently transcribed gene pairs representing more than 10% of

> the human genome, whose transcriptional start sites are separated by less than 1 kb. In addition, it has been suggested that more than half of the human promoters does not exhibit strong directionality in transcript initiation and can function in a bidirectional fashion. Thus, the synthetic bidirectional promoters of the present invention may mimic a well-represented and evolutionary conserved feature of eukaryotic transcription, providing a structural basis for their robust performance.
>
> More specifically, Chtarto et al. require the use of a transactivator factor encoded by a reverse antibiotic controlled transactivator nucleotide sequence for activating the bi-directional promoter. See, for instance, Chtarto et al. column 5, lines 12-16:
>
> > In said construct or system the bi-directional antibiotic controller activator responsive promoter/operator sequence 4 is advantageously activated by the transactivator factor 7, encoded by the reverse antibiotic controlled transactivator 7, encoded by the reverse antibiotic controlled transactivator nucleotide sequence 6 in the presence of said antibiotic 5.
>
> That Chtarto et al. is only directed to an antibiotic inducible/repressible genetic construct is clear throughout the document. See further Fig. 6, column 4, lines 42-43, column 5, lines 22-32.

Thus, Applicants argue that the "present invention offers the construction of a bidirectional promoter comprising a minimal viral promoter and a full length eukaryotic promoter", pointing to the description, page 7, lines 3-8:

> > A bidirectional promoter made by minimal core promoter elements from the human cytomegalovirus (mCMV) joined upstream, and in opposite orientation, to an efficient promoter, derived from the human phosphoglycerate kinase (PGK) or poly-ubiquitin UBI-C gene, was driving divergent transcription of two RNAs.

Applicants conclude that Chtarto et al do not anticipate the present invention "because Charto et al. do not teach each and every aspect of the present invention".

Applicants arguments have been fully considered but are respectfully not found persuasive for reasons of record and because Applicants arguments are not

commensurate with the scope of the claims, as written. For example, Applicants argument (just above) stating the "present invention offers the construction of a bidirectional promoter comprising a minimal viral promoter and a full length eukaryotic promoter" is not commensurate with the claim language of the amended base Claim 1 which does not refer to "a full length eukaryotic promoter" but instead refers to a first minimal promoter and "a promoter sequence of an animal gene comprising an enhancer region and a second minimal promoter sequence".

In addition, as discussed above, the proposed claim amendment submitted after final would not be remedial to applicants argument for reasons provided above.

In addition, the rejection of Claims 1, 3-4, 6-11 and 13-18 under 35 U.S.C. 102(e) as being anticipated by Itoh et al. (US 6,995,011, filed 7/3/2002, of record) is maintained for reasons of record and presented herein.

Applicants arguments have been fully considered but are respectfully not found persuasive for reasons of record and presented herein. Applicants' invention is as described above and see just above for description of proposed claim amendment. In addition, applicants claim a method for generating a transgenic non human organism comprising the step of transforming appropriate cells with an expression construct comprising the above recited bidirectional cassette and retroviral sequences as well as a method for coordinate expression of two exogenous coding sequences in a re-transplantable human hematopoietic cell.

Itoh et al. (see whole document, particularly Figs. 2-6, columns 7, 13, 15-16) teach retroviral expression vectors comprising a bi-directional promoter comprising two minimal CMV promoters (Tet responsive promoter) oriented in opposite directions as well as insertion sites for foreign sequences, polyadenylation sites downstream of the insertion sites and at least one IRES element. Itoh et al. also recite use of the construct for delivery and expression of multiple genes in re-transplantable animal (human) cells (can be hematopoietic cells) wherein the cells can be ex vivo. Itoh et al. also teach use of the expression vectors to generate transgenic animals by transforming appropriate cells with said expression vectors. Itoh et al. therefore teaches the claimed invention.

Applicants argue that Itoh et al is "directed exclusively to a vector comprising a low molecular weight compound-responsive bidirectional promoter and a DNA encoding a low molecular weight compound-controlled transactivator". Further, Applicants submit that "[i]n particular, the low molecular weight compound is tetracycline or doxycycline and the low molecular weight compound-controlled transactivator is a reverse tetracycline transactivator". Therefore, Applicants argue that "arguments presented above concerning Chtarto et al. are also valid in respect to Itoh et al." Applicants conclude that Itoh et al do not anticipate the present invention "because Itoh et al. do not teach each and every aspect of the present invention".

Applicants arguments are not commensurate with the scope of the claims, as written or with regards to the proposed claim amendment. Particularly, Applicants argument relies on Applicants argument (above) concerning Chtarto et al. However, as stated above, Applicants argument concerning Chtarto et al is not persuasive because

the argument is not commensurate with the scope of the claims, as written. For example, Applicants argument which states that the "present invention offers the construction of a bidirectional promoter comprising a minimal viral promoter and a full length eukaryotic promoter" is not commensurate with the claim language of the amended base Claim 1 which does not refer to "a full length eukaryotic promoter" but instead refers to a first minimal promoter and "a promoter sequence of an animal gene comprising an enhancer region and a second minimal promoter sequence".

In addition, as discussed above, the proposed claim amendment submitted after final would not be remedial to applicants argument for reasons provided above.

In addition, the rejection of Claims 1-4, 7-8, 10 and 14 under 35 U.S.C. 102(b) as being anticipated by Fux et al is maintained for reasons of record and herein.

Applicants arguments have been fully considered but are respectfully not found persuasive for reasons of record and presented herein. Applicants' invention is as described above and applicants proposed claim amendment is described above.

Fux et al. (cited by applicants, see whole article, particularly the paragraph bridging pp. 109-110, Table 1, Fig. 1, p. 114) teach bidirectional expression cassette systems comprising a minimal CMV promoter and a promoter derived from an animal gene (can be a minimal promoter) and a method for expression of multiple genes in animal (can be human) cells. Fux et al. therefore teaches the claimed invention.

Applicants argument that "Fux et al. discloses the construction of two vectors, PDuoRex7 and pDuoRex8 (see page 114, left column, last paragraph) which contain

two antibiotic-responsive expression units in divergent orientation. Such pDuoRex-based dual regulated expression requires concomitant production of tTA and PIT (see page 114, right column, first paragraph)" is not persuasive. Applicants submit that Applicants arguments presented above concerning Chtarto et al. "are also valid in respect to Fux et al". Applicants conclude that "Fux et al. do not anticipate the present invention because Fux et al. do not teach each and every aspect of the present invention".

In addition, Applicants submit the following regarding the prior art rejections:

> It should be noted that none of the cited prior art documents discloses a bidirectional promoter comprising a minimal viral promoter and a full length animal promoter. Therefore none of the cited documents anticipate the present invention.
>
> Moreover, starting from the teaching of Chtarto et al., or Itoh et al. or Fux et al. and due to the evolutionary distance between prokaryotes and mammalians and to their differences in the transcriptional machinery, the person skilled in the art would not predict and foresee that mammalian promoters could be also exploited for building a bidirectional promoter.

Therefore, Applicants state that "the invention is not obvious in respect to such cited prior art documents".

Applicants arguments have been fully considered but are respectfully not found persuasive for reasons of record and because Applicants arguments are not commensurate with the scope of the claims, as written. Particularly, Applicants argument relies on Applicants argument (above) concerning Chtarto et al. However, as stated above, Applicants argument concerning Chtarto et al is not persuasive because the argument is not commensurate with the scope of the claims, as written. For example, Applicants argument which states that the "present invention offers the

construction of a bidirectional promoter comprising a minimal viral promoter and a full length eukaryotic promoter" is not commensurate with the claim language of the amended base Claim 1 which does not refer to "a full length eukaryotic promoter" but instead refers to a first minimal promoter and "a promoter sequence of an animal gene comprising an enhancer region and a second minimal promoter sequence".

In addition, as discussed above, the proposed claim amendment submitted after final would not be remedial to applicants argument for reasons provided above.

In addition, the rejection of Claim 5 under 35 U.S.C. 103(a) as being unpatentable over Chtarto et al. or Itoh et al., either in view of Hope et al. (US 6,136,597, of record) is maintained for reasons of record and presented herein.

Applicants arguments have been fully considered but are respectfully not found persuasive for reasons of record and below.

Applicants' invention is as described above. In addition, applicants recite that the expression construct comprises a post-transcriptional regulatory element positioned upstream to one or each of the polyA sites.

Chtarto et al. and Itoh et al. are applied as above. Neither teaches inclusion of a post-transcriptional regulatory element positioned upstream to one or each of the poly A sites.

Hope et al. (see whole document, particularly the Abstract, last paragraph in column 2, column 3, column 16) teaches that inclusion of a post-transcriptional element such as a WPRE can enhance expression of a transgene in a target cell.

The ordinary skilled artisan, seeking to increase expression of a transgene, in cells transduced with a bi-directional expression vector system would have been motivated to combine the teachings of Chtarto et al. or Itoh et al. on the generation of expression vectors with bi-directional promoters with the teachings of Hope et al. on inclusion of WPRE elements in expression systems because Hope et al. teaches that inclusion of post-transcriptional elements such as WPREs increases the expression of transgenes contained in the vectors. It would have been obvious for the ordinary skilled artisan to do this because of the expected beneficial effect of increasing expression of the transgene(s) contained in the expression vectors. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Applicants argue that the combination of references would not teach or suggest all the features of the dependent Claim 5. For example, Applicants argument states (see page 12 of REMARKS, filed 17 March 2008) the "the combined teaching of Chtarto, Itoh and Hope does not teach or suggest constructing a bidirectional promoter comprising a minimal viral promoter and a full length animal promoter".

Applicants arguments have been fully considered but are respectfully not found persuasive for reasons of record and because Applicants arguments are not commensurate with the scope of the claims, as written. For example, Applicants argument states (see page 12 of REMARKS, filed 17 March 2008) the "the combined

teaching of Chtarto, Itoh and Hope does not teach or suggest constructing a bidirectional promoter comprising a minimal viral promoter and a full length animal promoter" is not commensurate with the claim language of the amended base Claim 1 which does not refer to "a full length animal promoter" but instead refers to a first minimal promoter and "a promoter sequence of an animal gene comprising an enhancer region and a second minimal promoter sequence".

In addition, as discussed above, the proposed claim amendment submitted after final would not be remedial to applicants argument for reasons provided above.

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